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Docket No.: 022290.0120PTUS
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Catherine Castan et al.

Application No.: 10/510,643 | Confirmation No.: 1869

Filed: May 23, 2005 | Art Unit: 1615

For: ORAL PHARMACEUTICAL FORMULATION IN THE FORM OF AN AQUEOUS SUSPENSION OF MICROCAPSULES FOR THE MODIFIED RELEASE OF ACTIVE PRINCIPLE(S) | Examiner: C. E. Helm

DECLARATION OF PHILIPPE CAISSE

1. My name is Philippe CAISSE.

2. I have been an employee of Flamel Technologies since 1991.

3. My position at Flamel Technologies is senior scientist at the Oral Forms Research Department.

4. I have a MSc in Polymer Science & Technology from Loughborough University.

5. I have worked in the area of pharmaceutical compositions for 19 years.

6. I consider myself to be one of skill in the art of oral pharmaceutical compositions for delayed and controlled release of active principles.

7. I supervised Damien Martinez, Rachid Boulmakoul and Jean-Luc Terrancle who prepared and tested the below two different compositions in accordance with the U.S. Application No.: 10/510,643 invention.

8. To the best of my knowledge, the information below is an accurate description of how these two compositions were prepared, and their release profiles measured.

9. The following examples present different coated active pharmaceutical ingredients with total percent of soluble compositions of the coating to all compositions of the coating comprised between 10 and 20%

10. Composition 1 was formed of the active ingredient ibuprofen, coated with an insoluble polymer P1 Ethocel 20 Premium (ethylcellulose), a soluble polymer P2 Plasdone K29/32 (polyvinylpyrrolidone), and an insoluble plasticizer castor oil, in the following weight fractions 80/10/10. The total percent of soluble compositions of the coating to all compositions of the coating is 10%.

11. Composition 2 was formed of the active ingredient amoxicillin, coated with an insoluble polymer P1 Ethocel 8 Premium (ethylcellulose), a soluble polymer P2 Kollidon K30 (polyvinylpyrrolidone), an insoluble plasticizer castor oil and a soluble surfactant Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil), in the following weight fractions 72/14/10/4. The total percent of soluble compositions of the coating to the total compositions of the coating is 18%.

12. Figures 1 – 2 below demonstrate that compositions keep similar their release profile, after few weeks of storage at ambient temperature in a liquid suspension vehicle which was not saturated initially with the active ingredient. The preparation of the two composition and the suspensions made from are detailed hereafter.

13. Composition 1

a. Composition 1 was prepared as follows:

i. 50 g of hydroxypropylcellulose (Klucel® EF) and 425 g of ibuprofen were dissolved in 1167 g of acetone. 25 g of talc were then dispersed in the solution. The suspension was entirely sprayed onto 500 g of cellulose spheres (Celphere® CP203 from Asahi Kasei) in a fluid bed spray coater apparatus Glatt® GPCG1.1. The obtained microgranules were sieved on screen with aperture of 500 µm. Microgranules with size below 500 µm were retained.

ii. 7.5 g of castor oil and 7.5 g of polyvinylpyrrolidone (Plasdone K29/32®) were dissolved in 517.5 g of acetone and 345.0 g of isopropyl alcohol. 60.0 g of ethyl cellulose (Ethocel 20 Premium) were then added and the solution was stirred until full dissolution. The solution was sprayed entirely onto 300.0 g of the above prepared microgranules in a fluid bed spray coater apparatus Glatt® GPCG1.1 with inlet temperature 35°C, spraying rate between 5 and 10 g per min and

atomization pressure 1.8 bar. Coated microparticles with mean diameter of 373 µm were obtained.

b. Suspension of composition 1 was prepared as follows:

   i. A quantity of composition 1 corresponding to 200 mg ibuprofen was added to 10ml of a 2.0 g/l solution of xanthane (Rodigel Easy®) in pH 4.5 medium (monobasic potassium phosphate buffer 0.05M).

c. Composition 1 and corresponding suspension were tested as follows:

   i. The microparticles and the microcapsule suspension stored one month at room temperature, were tested in a type II dissolution apparatus according to the Pharmacopoeia at a concentration of 200 mg ibuprofen in 900 ml of pH 6.8 medium (monobasic potassium phosphate buffer 0.05M) maintained at 37.0 ± 0.5 °C , agitated by a rotating paddle at 100 rpm.

d. The release profiles of Composition 1 microparticles and of the corresponding suspension stored one month at room temperature are shown in Figure 1. Among several methods investigated for dissolution profile comparison, f_2 is the simplest[1]. The calculation of the f_2 similarity factor was carried out using the following formula where R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the two curves:

$$f_2 = 50 \cdot \log \{[1+(1/n)\Sigma_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \cdot 100\}$$

e. The FDA has set a public standard of f_2 value between 50 to 100, to indicate similarity between two dissolution profiles.

   The value calculated is: $f_2 = 73$

   Both profile curves are thus similar, showing the stability of the release kinetics preserved by the microparticles even in the liquid suspension.

[1] V.P. Shah, Y. Tsong and P. Sathe (1998) In vitro dissolution profile comparison - statistics and analysis of the similarity factor, f_2. - *Pharm. Res.* **15**: 889-896.

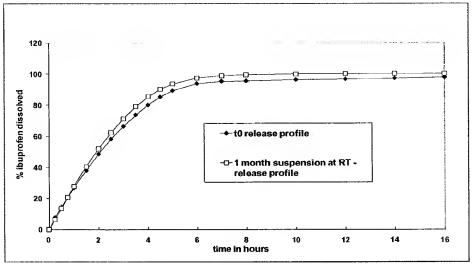


Figure 1

14. Composition 2

a. Composition 2 was prepared as follows:

i. A suspension composed of hydroxypropylcellulose (Klucel® EF) and amoxicillin in 70% isopropyl alcohol / 30% water was sprayed onto cellulose spheres (SCP100 from Asahi Kasei) in a fluid bed spray coater apparatus Glatt® GPCG1.1 to obtain microgranules with amoxicillin content about 80%. These granules were sieved on screens with 180 and 500 µm apertures. Microgranules with size comprised between 180 and 500 µm were retained.

ii. 6.52 g of castor oil, 2.61 g of polyoxyl 40 hydrogenated castor oil (Cremophor RH 40) and 9.13 g of polyvinylpyrrolidone (Plasdone K29/32®) were dissolved in 524.7 g of ethanol and 224.9 g of water. 46.93 g of ethyl cellulose (Ethocel 20 Premium) were then added and the solution was stirred until full dissolution. The solution was sprayed entirely onto 478.0 g of the above prepared microgranules in a fluid bed spray coater apparatus Glatt® GPCG1.1 with spraying rate 14 g per min and atomization pressure 1.7 bar. Coated microparticles with mean diameter of 381 µm were obtained

b. Suspension of composition 2 was prepared as follows:

i. 0.8 g of composition 2 microparticles was added to 5.0 g of water.

c. Suspension of composition 2 was tested as follows:

i. The suspension was tested in a type II dissolution apparatus according to the Pharmacopoeia at a total concentration of 500mg amoxicillin in 900 ml of pH 6.8 medium (monobasic potassium phosphate buffer 0.05M) maintained at 37.0 ± 0.5 °C , agitated by a rotating paddle at 100 rpm.

ii. The suspension was tested initially after its preparation and after two and ten days of storage at room temperature.

d. The release profiles of Composition 2 suspension initially and after storage at room temperature are shown in Figure 2.

The f_2 value calculated between the initial curve and the one obtained after two days of storage is: $f_2 = 97$

The f_2 value calculated between the initial curve and the one obtained after ten days of storage is: $f_2 = 84$

Thus, all curves are showing the stability of the release kinetics preserved by the microparticles even in the liquid suspension.

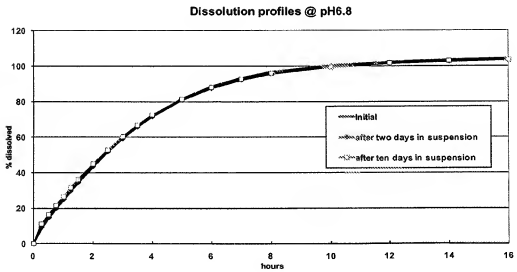
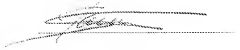


Figure 2

15. I declare that all statements made of my own knowledge are true and all statements, made on information and belief, are believed to be true. I make this declaration with the understanding that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the patent application.



Philippe CAISSE October 15, 2010